



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,369	07/27/2001	Douglas J. Dellinger	10003869-1	7604

7590 04/06/2004

AGILENT TECHNOLOGIES, INC.
Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599

EXAMINER

LEWIS, PATRICK T

ART UNIT PAPER NUMBER

1623

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/916,369	Applicant(s) DELLINGER ET AL.	
	Examiner Patrick T. Lewis	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 12-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-11) in Paper No. 12 dated June 9, 2003 is acknowledged.
2. Claims 12-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12 dated June 9, 2003.
3. This application contains claims 12-25 drawn to an invention nonelected without traverse in Paper No. 12 dated June 9, 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's Response dated January 13, 2004

4. In the Response filed January 13, 2004, claim 26 was added. Applicant presented arguments directed to the rejection of claims 1-5 and 8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention and the rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over the combination of Dellinger et al. U.S. Patent 6,222,030 (Dellinger), Crameri et al. U.S. Patent 6,376,246 (Crameri), and Manoharan et al. U.S. Patent 6,207,819 (Manoharan).

5. Claims 1-26 are pending. Claims 12-25 are drawn to a nonelected invention. An action on the merits of claims 1-11 and 26 is contained herein below.

6. The rejection of claims 1-5 and 8 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of applicant's arguments filed January 13, 2004.

7. The rejection of claims 1-11 under 35 U.S.C. § 103(a), is maintained for the reasons of record set forth in the Office Action dated September 9, 2003.

Objections/Rejections of Record Set Forth in Office Action

Dated September 9, 2003

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Dellinger et al. U.S. Patent 6,222,030 (Dellinger), Crameri et al. U.S. Patent 6,376,246 (Crameri), and Manoharan et al. U.S. Patent 6,207,819 (Manoharan).

Claims 1-11 are drawn to a method of synthesizing a polynucleotide, comprising (a) coupling a second nucleoside to a first nucleoside through a phosphite linkage, wherein the second nucleoside has a non-carbonate protecting group protecting a hydroxyl; and (b) exposing the product of step (a) to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl or the second nucleoside.

Dellinger teaches a method for synthesizing oligonucleotides using carbonate protection of hydroxyl groups and nucleophilic deprotection reagents (Abstract; column

4, lines 16-55). The deprotection reagents irreversibly cleave the carbonate protecting groups while simultaneously oxidizing the internucleotide phosphite triester linkage, and can be used in aqueous solution at neutral to mildly basic pH. The invention is premised on the discovery that rapid and selective removal of suitable 5'-OH or 3'-OH protecting groups following phosphoramidite condensation can be achieved by employing nucleophiles, and particularly peroxy anion, that exhibit an "alpha effect" under neutral or mildly basic conditions. In a preferred embodiment, the nucleophilic deprotection reagent that exhibits an alpha effect is a peroxide or a mixture of peroxides (column 11, lines 43-67; column 12, lines 1-24). The peroxide may be either inorganic or organic. Suitable inorganic peroxides include those of the formula M^+OOH^- , where M is any counter anion, including H^+ , Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ , or the like. Suitable organic peroxides include those of the formula $ROOH$, where R is selected from the group consisting of alkyl, aryl, substituted alkyl and substituted aryl. More particularly, the organic peroxide will have one of the general structures (V), (VI), or (VII). The two-step process of coupling and deprotection/oxidation is repeated until the oligonucleotide having the desired sequence and length is obtained (column 14, lines 52-56).

Dellinger differs from the instantly claimed method in that Dellinger: 1) does not teach the use of non-carbonate protecting groups; 2) does not teach the deprotection/oxidation step in non-aqueous solutions; and 3) does not teach composition comprising an acid for the removal of the non-carbonate protecting group. However, these deficiencies would have been obvious to the skilled artisan at the time of the invention when viewed in combination with Crameri and Manoharan.

Crameri teaches that codon-varied oligonucleotides are synthesized employing phosphoramidite solid-phase chemical synthesis in which the 3' ends of nucleic acid substrate sequences are covalently attached to a solid support, e.g., control pore glass (column 16, lines 59-67; column 17, lines 1-8). The 5' protecting groups can be a triphenylmethyl group, such as dimethoxytrityl (DMT); a carbonyl-containing group, such as Fmoc or levulinoyl; an acid-clearable group, such as pixyl; or a fluoride-cleavable alkylsilyl group, such as t-butyl dimethyl silyl (TBDMS), triisopropyl silyl, or trimethylsilyl.

Manoharan teaches methods for the preparation of mixed backbone oligomeric compounds (oligonucleotides). The method comprises coupling a first and a second nucleoside wherein said second nucleoside contains a 5'-OH protecting group. Next, the extended compound is treated with an oxidizing solution. A wide variety of hydroxy protecting groups can be employed in the methods of the invention (column 11, lines 49-67; column 12, lines 1-2). Preferably, the protecting group is stable under either acidic or basic conditions. Preferred protecting groups include dimethoxytrityl (DMT), monomethoxytrityl (MMT), 9-phenylxanthen-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthen-9-yl (Mox). Useful oxidizing agents include iodine/tetrahydrofuran/water pyridine, hydrogen peroxide/water, tert-butyl hydroperoxide or any peracid like m-chlorobenzoic acid (column 12, lines 57-65). The oxidizing solution generally has from about 18% to about 45% oxidizing agent, from about 2% to about 15% water [applicant defines a solutions as being substantially anhydrous when the solution is less than 5% water (page 25, lines 14-35)], from about 40% to about 80%

aprotic organic solvent, from about 0.01 M to about 0.8 M base dissolved in the aprotic organic solvent (column 14, lines 1-15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a polynucleotide, comprising (a) coupling a second nucleoside to a first nucleoside through a phosphite linkage, wherein the second nucleoside has a non-carbonate protecting group protecting a hydroxyl; and (b) exposing the product of step (a) to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl or the second nucleoside. The selection of a known material based on its suitability for its intended use is *prima facie* obvious. *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, although the method of Dellinger is limited to the use of carbonate protecting groups, Cramer teaches the suitability of both carbonate and non-carbonate protecting groups in oligonucleotide synthesis. The selection of an appropriate protecting group compatible with pendant functional groups and downstream reaction conditions is well within the purview of the skilled artisan. It would have also been obvious to the skilled artisan to employ a peroxide such as hydrogen peroxide or t-butyl hydroperoxide or any acid like m-chlorobenzoic acid to oxidize the phosphite internucleoside linkages as taught by Manoharan. Since compounds and their properties are inseparable, the protecting groups would also be removed during oxidation. One of ordinary skill in the art would have been motivated to do so in order to reduce the number of methodological steps.

Applicant's arguments filed January 13, 2004 have been fully considered but they are not persuasive. Applicant argues that the examiner has failed to present a prima facie case of obviousness asserting that combining references without sufficient suggestion of how to do so leads to error, and simply begs the question of how to arrive at the claimed method given the cited references.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As set forth supra, Dellinger teaches a method for synthesizing oligonucleotides employing deprotection reagents that irreversibly cleave the protecting groups while simultaneously oxidizing the internucleotide phosphite triester linkage. In a preferred embodiment, the nucleophilic deprotection/oxidation reagent is a peroxide or a mixture of peroxides. The peroxide may be either inorganic or organic. Dellinger uses carbonate-protecting groups, as opposed to non-carbonate protecting groups as instantly claimed, for the protection of 3'- or 5'-hydroxyl groups; however, as demonstrated by the prior art, both carbonate and non-carbonate protecting groups are routinely used in oligonucleotide synthesis to protect 3'- or 5'-hydroxyl groups. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discover

by applicant. In the instant case, it would have been obvious to one of ordinary skill in the art at the time of the invention to select a non-carbonate group to protect hydroxyl groups during oligonucleotide synthesis as the use of both (carbonate and non-carbonate) protecting groups have clearly been established by the prior art. It would have also been obvious to one of ordinary skill in the art at the time of the invention to oxidize the phosphite linkages to phosphate linkages using peroxides as taught by Dellinger. In the absence of some proof of a secondary nature to obviate the rejection as set forth in the Office Action dated September 9, 2003, or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, the instant rejection is deemed proper and is maintained.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Dellinger et al. U.S. Patent 6,222,030 (Dellinger), Crameri et al. U.S. Patent 6,376,246 (Crameri), and Manoharan et al. U.S. Patent 6,207,819 (Manoharan).

Claim 26 is drawn to a method of synthesizing a polynucleotide, comprising (a) coupling a second nucleoside to a first nucleoside through a phosphite linkage, wherein the second nucleoside has a non-carbonate protecting group protecting a hydroxyl; and (b) exposing the product of step (a) to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl or the second nucleoside.

Dellinger teaches a method for synthesizing oligonucleotides using carbonate protection of hydroxyl groups and nucleophilic deprotection reagents (Abstract; column 4, lines 16-55). The deprotection reagents irreversibly cleave the carbonate protecting groups while simultaneously oxidizing the internucleotide phosphite triester linkage, and can be used in aqueous solution at neutral to mildly basic pH. The invention is

premised on the discovery that rapid and selective removal of suitable 5'-OH or 3'-OH protecting groups following phosphoramidite condensation can be achieved by employing nucleophiles, and particularly peroxy anion, that exhibit an "alpha effect" under neutral or mildly basic conditions. In a preferred embodiment, the nucleophilic deprotection reagent that exhibits an alpha effect is a peroxide or a mixture of peroxides (column 11, lines 43-67; column 12, lines 1-24). The peroxide may be either inorganic or organic. Suitable inorganic peroxides include those of the formula M^+OOH^- , where M is any counter anion, including H^+ , Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ , or the like. Suitable organic peroxides include those of the formula $ROOH$, where R is selected from the group consisting of alkyl, aryl, substituted alkyl and substituted aryl. More particularly, the organic peroxide will have one of the general structures (V), (VI), or (VII). The two-step process of coupling and deprotection/oxidation is repeated until the oligonucleotide having the desired sequence and length is obtained (column 14, lines 52-56).

Dellinger differs from the instantly claimed method in that Dellinger does not teach the use of non-carbonate protecting groups. However, this deficiency would have been obvious to the skilled artisan at the time of the invention when viewed in combination with Crameri and Manoharan.

Crameri teaches that codon-varied oligonucleotides are synthesized employing phosphoramidite solid-phase chemical synthesis in which the 3' ends of nucleic acid substrate sequences are covalently attached to a solid support, e.g., control pore glass (column 16, lines 59-67; column 17, lines 1-8). The 5' protecting groups can be a triphenylmethyl group, such as dimethoxytrityl (DMT); a carbonyl-containing group,

such as Fmoc or levulinoyl; an acid-clearable group, such as pixyl; or a fluoride-cleavable alkylsilyl group, such as t-butyl dimethyl silyl (TBDMS), triisopropyl silyl, or trimethylsilyl.

Manoharan teaches methods for the preparation of mixed backbone oligomeric compounds (oligonucleotides). The method comprises coupling a first and a second nucleoside wherein said second nucleoside contains a 5'-OH protecting group. Next, the extended compound is treated with an oxidizing solution. A wide variety of hydroxy protecting groups can be employed in the methods of the invention (column 11, lines 49-67; column 12, lines 1-2). Preferably, the protecting group is stable under either acidic or basic conditions. Preferred protecting groups include dimethoxytrityl (DMT), monomethoxytrityl (MMT), 9-phenylxanthene-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthene-9-yl (Mox). Useful oxidizing agents include iodine/tetrahydrofuran/water pyridine, hydrogen peroxide/water, tert-butyl hydroperoxide or any peracid like m-chlorobenzoic acid (column 12, lines 57-65). The oxidizing solution generally has from about 18% to about 45% oxidizing agent, from about 2% to about 15% water [applicant defines a solution as being substantially anhydrous when the solution is less than 5% water (page 25, lines 14-35)], from about 40% to about 80% aprotic organic solvent, from about 0.01 M to about 0.8 M base dissolved in the aprotic organic solvent (column 14, lines 1-15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a polynucleotide, comprising (a) coupling a second nucleoside to a first nucleoside through a phosphite linkage, wherein the second nucleoside has a

non-carbonate protecting group protecting a hydroxyl; and (b) exposing the product of step (a) to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl or the second nucleoside. The selection of a known material based on its suitability for its intended use is *prima facie* obvious. *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, although the method of Dellinger is limited to the use of carbonate protecting groups, Cramer teaches the suitability of both carbonate and non-carbonate protecting groups in oligonucleotide synthesis. The selection of an appropriate protecting group compatible with pendant functional groups and downstream reaction conditions is well within the purview of the skilled artisan. It would have also been obvious to the skilled artisan to employ a peroxide such as hydrogen peroxide or t-butyl hydroperoxide or any acid like m-chlorobenzoic acid to oxidize the phosphite internucleoside linkages as taught by Manoharan. Since compounds and their properties are inseparable, the protecting groups would also be removed during oxidation. One of ordinary skill in the art would have been motivated to do so in order to reduce the number of methodological steps.

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a polynucleotide, comprising (a) coupling a second nucleoside to a first nucleoside through a phosphite linkage, wherein the second nucleoside has a non-carbonate protecting group protecting a hydroxyl; and (b) exposing the product of step (a) to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl or the second nucleoside. The

selection of a known material based on its suitability for its intended use is *prima facie* obvious. *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, although the method of Dellinger is limited to the use of carbonate protecting groups, Crameri teaches the suitability of both carbonate and non-carbonate protecting groups in oligonucleotide synthesis. The selection of an appropriate protecting group compatible with pendant functional groups and downstream reaction conditions is well within the purview of the skilled artisan.

The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discover by applicant. In the instant case, it would have been obvious to one of ordinary skill in the art at the time of the invention to select a non-carbonate group to protect hydroxyl groups during oligonucleotide synthesis as the use of both (carbonate and non-carbonate) protecting groups have clearly been established by the prior art. It would have also been obvious to one of ordinary skill in the art at the time of the invention to oxidize the phosphite linkages to phosphate linkages using peroxides as taught by Dellinger.

Conclusion

14. Claims 1-26 are pending. Claims 12-25 are drawn to a nonelected invention. Claims 1-11 and 26 are rejected. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

Art Unit: 1623

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

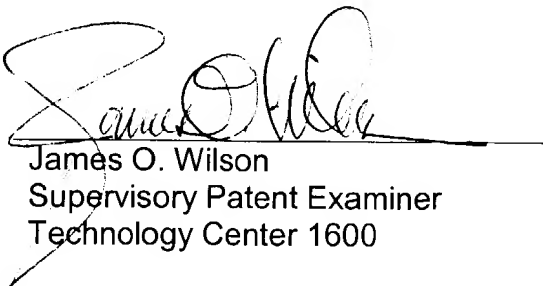
Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on M-F 10:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
April 5, 2004